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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,171	12/08/2005	Hagit Eldar-Finkelman	29724	4524

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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,171	ELDAR-FINKELMAN, HAGIT	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) *186* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,7,8,10,11,14-17,24-26,28,46-49,63-65,67,71-74,88-90,93-99,101,118-125,127-129,131-135,141-146,148-150,152-156,162,163 and 179-186.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 90,93-96,118-125,127-129,131-135,141-146,148-150,152-156 and 162.

Continuation of Disposition of Claims: Claims rejected are 1,2,7,8,10,11,14-17,24-26,28,46-49,63-65,67,71-74,88,89,97-99,101,163 and 179-185.

1. Applicant's election of the species treatment of non-insulin dependent diabetes mellitus, in the reply filed on July 5, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 90, 93-96, 118-125, 127-129, 131-135, 141-146, 148-150, 152-156, and 162 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 5, 2007.

2. The disclosure is objected to because of the following informalities: At pages 7, 14, 15, and 23 of the specification, the meaning of the circled words "Deleted: X" is not known. It is not clear if these words are to be inserted into the specification, or if these words indicate that "X" has been deleted from the paragraph. The amendment format is not compliant with 37 CFR 1.121(b). Appropriate correction is required.

The substitute specification filed December 14, 2007 has not been entered because it does not conform to 37 CFR 1.125(b) and (c). A marked-up copy of the substitute specification has not been supplied (in addition to the clean copy). See also MPEP 608.01(q).

3. Instant claims 1, 2, 7, 8, 10, 11, 14-17, 24-26, 28, 46-49, 63-65, 67, 71-74, 88, 89, 97-99, 101, 163, and 179-186 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional applications 60/432,644 and 60/482,719, because the provisional applications, under the test of 35 U.S.C. 112, first paragraph, do not disclose, e.g., conjugates of the general formula recited in independent claim 1 where the hydrophobic moiety can be attached to any part of the polypeptide, or conjugates of the general formula recited in

independent claims 46, 71, and 88, where n can range from 16 to 50 and where the hydrophobic moiety can be attached to any part of the polypeptide, or conjugates of the general formula recited in independent claim 179 where the hydrophobic moiety is the hydrophobic peptide as defined in the claim. Accordingly, the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980) is available as prior art against the instant claims under 35 U.S.C. 102(a).

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1, 2, 7, 8, 10, 11, 14, 15, 46-49, 63-65, 71-74, 88, and 89 are rejected under 35 U.S.C. 102(a) as being anticipated by the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980). The Plotkin et al article teaches a GSK-3 inhibitor designated L803-mts and having the structure recited in Applicant's claims, i.e. comprising a N-terminal myristoyl group, an alanine residue at the positions corresponding to Applicant's Z and Y_3 residues, n=6, and m=1. See page 975, column 2, second full paragraph. L803-mts has the same amino acid sequence as Applicant's SEQ ID NO:16. L803-mts also corresponds to the structure recited in Applicant's claims in which n=1 and the N-terminal sequence GKEAP comprises a hydrophobic peptide sequence AP. The inhibitor is dissolved in 0.1% DMSO buffer solution (see page 975, column 1, second full paragraph), which corresponds to Applicants' pharmaceutically acceptable carrier. The inhibitor inhibits the ability of GSK-3 to phosphorylate a peptide substrate; is administered in vitro to HEK 293 cells and to mouse adipocytes, optionally followed by contacting the mouse adipocytes with suboptimal amounts of insulin; and is administered to insulin-resistant obese mice and improves their glucose tolerance. See, e.g., the Abstract; page

975, column 2, second full paragraph, through page 976, column 1, second full paragraph; and Figure 1.

6. Claims 16, 17, and 163 are rejected under 35 U.S.C. 103(a) as being obvious over the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980). Application of the Plotkin et al article is the same as in the above rejection of claims 1, 2, 7, 8, 10, 11, 14, 15, 46-49, 63-65, 71-74, 88, and 89. The Plotkin et al article does not teach packaging the L803-mts with instructions for use. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to package the L803-mts with instructions for use because it is routine to package pharmaceutical compositions with instructions for use because it eases storage, transportation, measurement, and administration of the pharmaceutical composition. The Plotkin et al article does not teach forming L803-mts by reacting myristic acid with the peptide portion of the inhibitor. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the L803-mts of the Plotkin et al article by reacting myristic acid with the peptide portion of the inhibitor, because peptide conjugates are routinely formed in the art by reacting the peptide portion of the conjugate with the modifying agent, and because the method of synthesis would not have been expected to affect the activity of the resulting peptide conjugate.

7. Claims 24-26, 28, 63-65, 67, 97-99, and 101 are rejected under 35 U.S.C. 103(a) as being obvious over the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980) as applied against claims 1, 2, 7, 8, 10, 11, 14, 15, 46-49, 63-65, 71-73, 88, and 89 above, and further in view of the American Diabetes Association article (Diabetes Care, Vol. 17, pages 616-623) or the WO Patent Application 01/49709. The Plotkin et al article does not teach co-

administration of GSK-3 inhibitors such as insulin and ingredients capable of downregulating an expression of GSK-3 when administering L803-mts in vivo. The American Diabetes Association article teaches insulin administration as a standard practice when treating patients with NIDDM. See page 617, column 3, first full paragraph. The WO Patent Application '709 teaches co-administering ingredients capable of downregulating an expression of GSK-3 when treating patients with NIDDM. See, e.g., page 19, line 17 - page 20, line 10. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to combine treatment with L803 as taught by the Plotkin et al article and treatment with insulin as taught by the American Diabetes Association article or treatment with ingredients capable of downregulating an expression of GSK-3 as taught by the WO Patent Application '70-9, because co-administration of active agents when treating NIDDM is known as taught by the American Diabetes Association article and by the WO Patent Application '709, and because co-administration of active agents would have been expected to increase the probability of effective treatment.

8. Claims 46-49, 63-65, 67, 71-74, 88, 89, 97-99, 101, and 163 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 01/49709. The WO Patent Application '709 teaches a GSK-1 inhibitor, designated peptide #8 (see page 30, Table 1), which corresponds to Applicant's conjugate in which n=1, a hydrophobic moiety comprising the hydrophobic peptide sequence Ala-Pro is attached to the N-terminus of the polypeptide, m=1, and the residue corresponding to Applicants' Z residue is alanine. The WO Patent Application '709's inhibitors are combined with pharmaceutically acceptable excipients and carriers. See, e.g., page 18, lines 3-7, and page 20, lines 11-30. The inhibitors inhibit GSK-3 in vitro in cell-

based assays. See, e.g., Example 3 and claim 8. The inhibitors are used to potentiate insulin signaling and to treat non-insulin dependent diabetes mellitus. See, e.g., page 9, line 20 - page 10, line 9, and page 25, lines 7-29. The inhibitors can be co-administered with, e.g., lithium, which is a GSK-3 inhibitor, or an antisense or ribozyme molecule which downregulates expression of GSK-3. The inhibitors can be co-administered with insulin until insulin potentiation obviates the need for administration of exogenous insulin. See, e.g., page 19, line 17 - page 20, line 10; and Example 4. The WO Patent Application '709's peptide inhibitors can be synthesized by Merrifield synthesis (see page 15, lines 18-28), which will result in hydrophobic amino acids/moieties being attached to a peptide portion of the inhibitor corresponding to Applicant's polypeptide.

9. Claims 1, 2, 7, 8, 10, 11, and 179-182 are rejected under 35 U.S.C. 102(b) as being anticipated by the Taniguchi et al article (J. Biol. Chem., Vol. 269, pages 18299-18302). The Taniguchi et al article teaches the protein MARCKS (see Figure 3), which is myristoylated at the N-terminus. The myristoylated protein MARCKS corresponds to Applicant's conjugate in which Myr-GAQFSKTAAKGEAT is the hydrophobic moiety comprising the fatty acid and seven hydrophobic amino acids (G, A, F, A, A, G, and A); and in which the partial sequence AERPGEAAVASS*P corresponds to Applicant's polypeptide having the amino acid sequence in which n=7, Y_3 is G, Z is Ala, and m=1. The myristoylated protein MARCKS also comprises hydrophobic peptide sequences PAAAG, PAAAAP, GAAGA, GGAAAAAG, etc. which correspond to the at least one hydrophobic moiety of Applicant's claim 179 and which are attached indirectly to the C-terminus of the residues which correspond to Applicant's polypeptide. The additional amino acid residues which are present in the myristoylated protein

MARCKS of the Taniguchi et al article are permitted by Applicant's claim language which uses "comprising" to define the conjugate. These additional amino acid residues present in the myristoylated protein MARCKS form part of Applicant's claimed conjugate, but are in addition to the polypeptide recited in Applicant's claims. In view of the similarity in structure between the myristoylated protein MARCKS of the Taniguchi et al article and Applicant's claimed conjugates, inherently the protein MARCKS of the Taniguchi et al article will be capable of inhibiting an activity of GSK-3, and inherently the myristoyl group and/or hydrophobic peptide sequences present in the protein MARCKS of the Taniguchi et al article will provide the conjugate with better membrane permeability and/or interaction with the hydrophobic patch of GSK-3, to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the protein MARCKS of the Taniguchi et al article and Applicant's claimed conjugates to shift the burden to Applicant to provide evidence that the claimed conjugates are unobviously different than the protein MARCKS of the Taniguchi et al article.

10. Claims 1, 2, 7, 8, 10, 11, 15-17, and 179-185 are rejected under 35 U.S.C. 102(b) as being anticipated by the Manenti et al article (J. Biol. Chem., Vol. 267, pages 22310-22315) in view of the Taniguchi et al article (J. Biol. Chem., Vol. 269, pages 18299-18302). The Manenti et al article teaches an aqueous solution of MARCKS dialyzed against a 10 mM Tris-HCl aqueous solution. See, e.g., page 22311, column 1, second full paragraph. Application of the Taniguchi et al article is the same as in the above rejection of claims 1, 2, 7, 8, 10, 11, and 179-182. The Taniguchi et al article, which incorporates by reference to the Manenti et al article (see page 18299, column 2, third full paragraph) shows that the MARCKS of the Manenti et al article anticipates Applicant's claimed conjugate. In addition, the Tris-HCl aqueous solution with

which the MARCKS of the Manenti et al article is combined meets Applicants' requirement for a pharmaceutically acceptable carrier as recited in instant claims 15 and 183. Note that an intended use limitation, i.e. the term "pharmaceutical" in the preamble to claims 15 and 183, does not impart patentability to product claims where the product is otherwise anticipated by the prior art. With respect to instant claims 16 and 184, the Tris-HCl aqueous solution comprising MARCKS of the Manenti et al article is inherently packaged, as containment of an aqueous solution inherently requires a package. With respect to Applicant's "identified in print..." limitations, note that nonfunctional printed matter does not distinguish a claimed product over an identical prior art product. See MPEP 2112.01(III).

11. Applicant's arguments filed December 14, 2007 have been fully considered but they are not persuasive.

No claims have been re-joined with the elected and examined invention, because no claim generic to the elected invention has yet been found to be allowable.

The examiner maintains his position that the instant claims are not entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional applications 60/432,644 and 60/482,719 for the reasons set forth in section 3 above. Accordingly, the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980) is available as prior art under 35 U.S.C. 102(a). Applicant contends that the Plotkin et al article does not disclose a peptide inhibitor beyond the subject matter disclosed previously by the provisional application '644. However, a claim for priority under 35 U.S.C. 119(e) does not concern a comparison of a prior art document with the disclosure of the provisional application; rather, what is compared is the claimed invention in the nonprovisional application with the disclosure of the provisional application. If

the disclosure of the provisional application does not adequately support and enable the invention claimed in the nonprovisional application, the nonprovisional application is not entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the provisional application. See MPEP 201.11(I). The instant claims are not adequately supported by the disclosure of the provisional application, for the reasons set forth in section 3 above, and accordingly the instant claims are not entitled to the benefit of the filing date of the provisional application. The relationship between the disclosure of the Plotkin et al article and the disclosure of the provisional application is irrelevant to the issue of priority under 35 U.S.C. 119(e). Applicant's attorney's statement at page 19, first full paragraph, does not satisfy the requirements of a Katz-type declaration under 37 CFR 1.132, as set forth in, e.g., MPEP 715.01(c)(I).

The WO Patent Application 01/49709 is not applied against independent claims 1 or 179, or against the claims dependent upon these claims. The WO Patent Application '709 does not teach or render obvious a peptide with a fatty acid to attached the peptide, as is required by instant claim 1, and does not teach or render obvious a peptide with a hydrophobic peptide sequence attached to the peptide, where the hydrophobic peptide sequence is as defined in instant claim 179.

The WO Patent Application 01/49709 continues to be applied against instant claims 46-49, 63-65, 67, 71-74, 88, 89, 97-99, 101, and 163. Note that the definitions of the variable n and of the hydrophobic moiety have not been modified in the latest version of these claims. The conjugate is defined using "comprising" language (see, e.g., claim 46, line 3), and therefore the presence of additional amino acid residues, e.g., the hydrophilic amino acids Glu-Lys present in peptide #8 of the WO Patent Application '709 are not excluded by Applicant's claim language.

Because peptide #8 of the WO Patent Application '709 meets all of the structural requirements recited in Applicant's claims, inherently the hydrophobic amino acids Ala-Pro present in peptide #8 will provide the conjugate with better membrane permeability and/or better interaction with the hydrophobic patch of GSK-3 to the same extent claimed by Applicant. The WO Patent Application '709 need not describe its peptide using the same terminology chosen by Applicant in order to anticipate Applicant's claims, and Applicant has not submitted any evidence demonstrating that peptide #8 of the WO Patent Application '709 does not possess one or more of the properties recited in Applicant's claims.

Claims 1, 2, 7, 8, 10, and 11 remain rejected, and new claims 179-182 are rejected, over the Taniguchi et al article (J. Biol. Chem., Vol. 269, pages 18299-18302). The amendments to the claims do not distinguish over the peptides taught by the Taniguchi et al article, i.e. do not exclude from the scope of the claims the additional amino acids which are present in the myristoylated protein MARCKS. Again, note the "comprising" language used by Applicant to define the claimed conjugates. With respect to instant claim 180, note that the claim does not specify that the at least one hydrophobic moiety is attached "directly" to the N-terminus and/or C-terminus of the polypeptide.

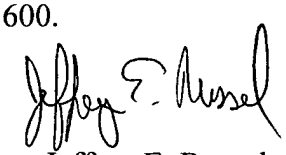
12. Claim 186 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel
February 4, 2008